

EDITORIAL COMMENT

Magnetic Resonance Imaging in Cardiac Amyloidosis*

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The amyloidoses are a group of uncommon systemic diseases characterized by the extracellular deposition of pathologic insoluble amyloid protein in organs and tissues. There are 4 main types of amyloidosis: primary (AL, the most prevalent type), familial, secondary, and senile. Each of them has its own physiopathology, distinctive features, and variable cardiac involvement. The symptoms of cardiac amyloidosis include atrial, atrioventricular, and ventricular conduction disturbances, ventricular and supraventricular arrhythmias, orthostatic symptoms, restrictive cardiomyopathy, angina, and heart failure.

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New therapies for cardiac amyloidosis have been recently introduced with promising results, and therefore, early diagnosis of cardiac amyloidosis is important, but can be very challenging. Endomyocardial biopsy (EMB) remains the gold standard diagnostic method (1), although clinically significant amyloid can be missed with small biopsies because of heterogeneous deposition. In practice, noninvasive tests are widely used to diagnose amyloidosis, including electrocardiography and echocardiography (2). Electrocardiography has limited diagnostic accuracy, which increases when it is combined with echocardiography. Echocardiography has some diagnostic limitations, however, particularly if left ventricular hypertrophy from other causes is present, and is usually normal until the patient is symptomatic. Finally, neither electrocardiography nor echocardiography can confirm the

diagnosis by itself, and they cannot confirm amyloidosis type.

Diagnosis

Late gadolinium-enhanced cardiovascular magnetic resonance (LGE-CMR) has value in the diagnosis of amyloid cardiomyopathy. Gadolinium chelates distribute in the extracellular space that is expanded by amyloid infiltration, leading to signal enhancement. The blood pool is unusually dark in these patients, probably reflecting high tissue uptake and fast blood pool washout. LGE was shown in 69% of patients with a characteristic global subendocardial diffuse pattern that agreed with the transmural histological distribution of amyloid protein in the myocardium and correlated with morphological markers of increased amyloid load (3). Furthermore, a T1 mapping method revealed abnormal gadolinium kinetics. An optimized threshold (191 ms at 4 min) between myocardial and blood showed an 88% accuracy in the diagnosis of cardiac amyloidosis. A patchy pattern of LGE can also occur. Other studies have confirmed the value of LGE for diagnosis (4,5). Although there is agreement that LGE-CMR is useful in diagnosing cardiac amyloidosis, it has not been compared with traditional noninvasive markers. In this issue of *JACC*, Austin et al. (6) report their study of diagnostic accuracy in 38 patients with EMB, LGE-CMR, clinical assessment, electrocardiography (ECG), and echocardiography (2-dimensional and Doppler). Of the 38 patients, 17 had EMB-proven cardiac amyloidosis. When compared with Carroll's low-voltage criteria, deceleration time <150 ms on Doppler, and New York Heart Association functional class status, LGE-CMR was the most accurate predictor of EMB-positive cardiac amyloidosis, with sensitivity, specificity, and positive and negative predictive values of 88%, 95%, 93%, and 90%, respectively, within the range of previously published reports and significantly

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higher than for the other tests. Despite these good results, the authors acknowledge that LGE-CMR may also have pitfalls. An early patchy subendocardial LGE, asymmetrical hypertrophy, or the coexistence of other conditions such as ischemic heart disease may lead to a false negative interpretation, as it was in the case with 2 patients in the present study. In addition, the LGE technique can be challenging in amyloidosis, and care must be taken when acquiring the images in order not to get confusing results, and it is here where assessment of T1 kinetics can be helpful.

Prognosis

The prognosis of amyloidosis is generally poor if untreated, and cardiac involvement is a marker of poor outcome. Thus, median survival for AL amyloidosis is 13 months without therapy and 17 months with melphalan, whereas only 5% of patients survive more than 10 years. When cardiac involvement is present, survival rate is even worse, with mean survival of 6 months after the onset of congestive heart failure. Therapy with high-dose intravenous melphalan plus autologous peripheral blood stem-cell transplantation has shown a 40% complete remission at 1 year and improved median survival to 4.6 years, which again decreases to 1.6 years if there is cardiac involvement. Cardiac transplantation in AL amyloid has shown 1- and 5-year survival rates of 60% and 30%, respectively. For familial amyloidosis, survival may be up to 15 years, and liver transplantation is nowadays the only definitive therapeutic intervention, combined or not with heart transplant. Senile amyloidosis has a better prognosis, with a median survival rate of 5 years. Finally, for AA amyloidosis, prognosis is usually determined by the underlying chronic disease, with a median survival from diagnosis of roughly 10 years.

A large number of prognostic parameters in amyloidosis have been reported in the past, including the presence of heart failure or syncope, elevation of troponins and N-terminal pro-B-type natriuretic peptide, complex ventricular arrhythmia on ambulatory ECG monitoring, low voltage on the ECG, and pulmonary hypertension (7). There are also a number of echocardiography-derived prognostic markers such as left ventricular ejection fraction, left ventricular wall thickness (inversely related to survival), right ventricular dilation, restrictive hemodynamics, myocardial performance index, and abnormalities in cycle-dependent variation of myocardial integrated backscatter (8,9). Currently, there is little agreement on which parameters are most predictive of outcome. A

recent study showed the only significant predictors of survival were left ventricular ejection fraction, low-voltage on the ECG, and etiology of amyloidosis. CMR has shown prognostic utility in amyloidosis (10). No differences in survival were seen according to the presence of LGE, but T1 kinetics showed that an intramyocardial T1 gradient <23 ms at 2 min and subepicardial-blood T1 difference <80 ms had an 85% and 90% accuracy, respectively, for predicting outcome. A likely explanation for the discrepancy between LGE and T1 kinetics is the superior discrimination by T1 kinetics for the severity and transmural-ity of the myocardial amyloid burden. The intramyocardial T1 gradient (subepicardium minus subendocardium T1), for which higher values indicate less gadolinium in the epicardium, and subepicardial minus blood T1 difference (again reflecting lower epicardial gadolinium uptake) were both higher in patients who survived. This is explained by the usual pattern of amyloid deposition in the myocardium, which is predominantly subendocardial with lower cardiac amyloid burden. The Austin et al. (6) report also assessed the prognostic value of LGE-CMR and found that it was the only significant predictor of 1-year mortality, whereas no echocardiographic parameter was predictive. There is a possible explanation for this discrepancy with previous CMR results. At 1 year, they found only 9 deaths (36%) among the biopsy-positive patients, which is better than previous survival figures. This may reflect either a different population with earlier disease, or the effect of recently implemented therapeutic protocols that have affected survival. It is plausible that LGE may have significant prognostic utility in early-stage amyloidosis, whereas for a more advanced stage of the disease, T1 kinetics may be more useful.

In summary, there is agreement on the diagnostic value of CMR in cardiac amyloidosis. Furthermore, LGE-CMR might help detect cardiac involvement in systemic amyloidosis when cardiac changes are not apparent in echocardiography. Screening of subclinical cardiac involvement may become possible should LGE prove to have adequate sensitivity and specificity in detecting amyloid infiltration. CMR also appears to be useful to assess prognosis. Further comparative studies are needed in well-defined clinical cohorts, and this will require a multicenter approach.

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